PERGAMON

Molecular Immunology 38 (2001) 1005–1006

Molecular Immunology

www.elsevier.com/locate/molimm

Editorial

To kill or not to kill

In this issue of *Molecular Immunology*, a series of review articles is devoted to the recent advance in the structure and function of natural killer (NK) and T-cell receptors as well as the breakthrough in the recognition of immunoglobulin by Fc receptors.

The cloning of killer immunoglobulin-like (KIR) and the C-type lectin-like (CTLR) NK cell receptors in the mid 1990s opened a new chapter in NK cell biology and transformed the field to the molecular immunology arena. Since then, more than a dozen of receptors have been cloned and the ligands for some have been identified. It has become clear now that the decision for NK cells to kill or not to kill hinges upon the balance between a set of inhibitory and activating receptors. Both KIR and CTLR families of inhibitory receptors recognize class I MHC molecules. Until recently, however, the only known structures of class I MHC recognizing receptors were those of T-cell receptors. The structure solutions of human KIR receptors in complex with its class I cognate HLA molecules and a murine Ly49 in complex with its MHC ligand provided first atomic view of how class I MHC molecules function in innate immunity. The review by Boyington and Sun describes the molecular recognition between KIR2DL2 and HLA-Cw3. In it, the authors offered structural interpretations of the known allotype specificities of KIR and of the role of MHC bound peptide in KIR recognition. A preformed crystal lattice KIR–HLA aggregation was proposed as a model to mimic the structure of the receptor mediated immune synapse. Unlike its human functional ortholog, the murine Ly49A recognizes its class I MHC ligand and in a very different structural mode. Natarajan et al. summarize the binding between Ly49A and H-2D^d. In addition, the authors provided the most recent evidence to clarify a long standing confusion generated by the original structural publication, in which two binding sites, dubbed sites 1 and 2 on H-2D^d, were proposed to interact with Ly49A.

Despite some KIR and Ly49 receptors possess activating isoforms that are capable of signaling through the ITAM containing molecule DAP12 and thus triggering target cells lysis in transfection systems, the in vivo role of theses activating isoforms remains unclear. To this end, several receptors have been identified that fit the ‘to kill’ category of NK receptors. One of them, notably, is NKG2D that has been shown to bind the stress and tumor induced ligands, including MICA/B and ULBPs in human and H60 and Rae-1 in mice. The review by Strong offers a comprehensive look at the recognition of NKG2D with two of its ligands, a human MICA and murine Rae-1. The recognition of another ligand, a human ULBP, by NKG2D is summarized in the review by Boyington and Sun.

Also in this issue are the reviews for the most recent structural development in T-cell receptor and Fc receptor signaling. Much of structural immunology has been propelled by the structural characterizations of T-cell receptors and MHC molecules in the last decade. The fall out from several of these heavy weight contests has been the atomic solution of T-cell receptors in complex with both class I and class I MHC molecules and much needed mechanistic insight to T-cell receptor activations. The quest for the holy Grail, the atomic anatomy of the entire multi-subunit TCR-MHC machinery, however, continues. Wang and Reinherz added their most recent contribution to this long journey, the solution of a TCR co-receptor CD4 in complex with a class II MHC and its bound peptide. Based on this work and their earlier structural work of TCR in complex with a class II MHC, they proposed a model for TCR, class II MHC and CD4 ternary complex. A newest addition to the structure of T-cell receptors is the recent solution of a γδ TCR. Although unliganded, the structure of the free receptor is an important contribution to the T-cell structural immunology. The article by Allison and Garboczi in this volume provides structural insights to the receptor function as well as its comparison with the known structures of αβ TCR.

The last two articles in this issue of *Molecular Immunology* review, the recognition of Fc receptors as described in two structures of Fc–Fc receptor complexes. Wurzburg and Jardetzky compared several structures of FcεRI derived from multiple crystal forms, described in detail the recognition between IgE-Fc and FcεRI. When the complex structure was compared with that of Fc, the authors concluded that conformational changes in Fc occurred upon complex formation with the receptor. Radaev and Sun described their work on a low affinity immunoglobulin receptor FcγRIII

0161-5890/02/$ – see front matter. Published by Elsevier Science Ltd.
PII: S0161-5890(02)00029-9

and its complex with an IgG-Fc. Based on the structure of the receptor–ligand complex, Radaev and Sun designed and tested peptide inhibitors that are capable of blocking the IgG binding to FcγRIII. The comparison between the high affinity IgE and the low affinity IgG-Fc receptor complexes underline the critical regions important for the receptor–ligand affinity.

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